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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,090	12/14/1999	AXEL ULLRICH	2923-0347	3321

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/461,090	Ullrich et al.,
Examiner	**Art Unit**
Frank Lu	1634

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *11/25/2002, 1/24/2003, and 2/21/2003*

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *22-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *22-36* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [X] All b) [ ] Some* c) [ ] None of:

1. [X] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on November 25, 2002 and supplemental response filed on January 24, 2003 and February 21, 2003 have been entered. The claims pending in this application are claims 22-36. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on November 25, 2002, January 24, 2003 and February 21, 2003.

Claim Objections

2. Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim since claim 27 does not further limit said receptor tyrosine kinase as recited in claim 23. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 22-34 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 23-34 are dependent on claim 22.

5. Claims 22 and 36 are rejected as vague and indefinite because it is unclear what is an extracellular G protein or an extracellular G protein coupled receptor initialed signal pathway. There is no definition for extracellular G protein or extracellular G protein coupled receptor initialed signal pathway in the specification. Please clarify.

6. Claim 32 is rejected as vague and indefinite because claim 22 and claim 32 are not correspond each other. Since claim 22 only has a cell having a receptor tyrosine kinase while the compound in claim 23 affects a cell which is different from the cell containing the receptor tyrosine kinase, claim 23 require another cell which is different from the cell containing the receptor tyrosine kinase as recited in claim 22 in order to perform the method in claim 22. However, there is no such cells in claims 22 and 32. Please clarify.

Claim Rejections - 35 USC § 102/103

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 22-36 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dong *et al.*, (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

Regarding claims 22-30 and 32-36, Dong *et al.*, teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor. As acknowledged by Dong *et al.*, ligands that activated the epidermal growth factor receptor (EGFR) were synthesized as membrane-anchored precursors as recited in claims 26 and 27 that appeared to be proteolytically released by members of the ADAM family of metalloproteases as recited in claims 28 and 29. This membrane-anchored EGFR ligands were thought to be biologically. In this study, they used metalloprotease inhibitors as recited in claims 24, 25, 28 and 29 to block EGFR ligand release from human mammary epithelial cells. These cells expressed both transforming growth factor α and amphiregulin and required autocrine signaling through the EGFR (extracellular domain) as recited in claims 23, 33, and 34 for proliferation and migration. They found that a metalloprotease inhibitor, batimastat as recited in claim 31 (see page 6236, Figure

1), reduced cell proliferation in direct proportion to their effect on transforming growth factor α release. This metalloprotease inhibitor also reduced growth of EGF-responsive tumorigenic cell lines and were synergistic with the inhibitory effects of antagonistic EGFR antibodies. Blocking release of EGFR ligands also strongly inhibited autocrine activation of the EGFR and reduced both the rate and persistence of cell migration. The effects of this metalloprotease inhibitor was reversed by either adding exogenous EGF or by expressing an artificial gene for EGF that lacked a membrane-anchoring domain (page 6235, abstract). The effect of batimastat on the activation of tyrosine phosphorylation as recited in claim 36 was also be examined (see page 6238, right column and Figure 4). Note that: (1) the phrase "a method for identifying compound for modulating growth receptor activation by G-protein-mediated signal transduction" in claim 20 is preamble and is not considered as the limitations in this rejection. Note that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951); (2) although Dong et al., does not directly show that their method is not related to modulate G-protein mediated signal transduction, they show that the level of EGFR tyrosine phosphorylation is reduced in the presence of a compound (ie., batimastat). Since it is known that reduction of tyrosine phosphorylation of a receptor is correlated to activation of G protein, batimastat used in the method of Dong *et al.*, also modulate G-protein mediated signal transduction.

Regrading claim 31, it is known that the ADAM family of metalloproteases used in the method of Dong *et al.*, are zinc-dependent proteinases.

Response to Arguments

In page 5, last paragraph bridging to page 6, first paragraph of applicant's remarks filed November 25, 2002, applicant argues that "[D]ong does not suggest or disclose a method for modulating G-protein mediated signal transduction," since "[D]ong's findings suggest that the proteins whose production is stimulated by EGFR are EGF-like ligand precursors and metalloproteases. In contract to Dong, the present inventions has identified GPCR ligands as mediators of autocrine signaling through EGFR.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, although Dong et al., does not directly show that their method is related to modulate G-protein mediated signal transduction, they show that the level of EGFR tyrosine phosphorylation is reduced in the presence of batimastat (ie., a compound recited in claims 22, 35, and 36). Since it is known that reduction of tyrosine phosphorylation of a receptor is correlated to G protein activation, besides regulating autocrine signaling, batimastat used in the method of Dong et al., also modulates G-protein mediated signal transduction. Applicant appears to agree that autocrine signaling through EGFR is mediated by G protein (see page 6, first paragraph of applicant's remarks filed on November 24, 2002). Second, Dong et al., teach all method steps recited in claims 22, 35, and 36.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No Claim is allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
May 16, 2003

Ethan Whisenant, Ph.D.
Primary Examiner (FSA)